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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/748,354	12/30/2003	Richard L. Moss	054030-0045	7816

31096 7590 09/19/2006

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EXAMINER	
SGAGIAS, MAGDALENE K	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 09/19/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/748,354	MOSS ET AL.	
	Examiner	Art Unit	
	Magdalene K. Sgagias	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *7/10/06*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8 and 14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8 and 14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-8 and 14 are pending and under consideration. Claims 9-13 are canceled.

Claim Objections

Applicant's arguments, see page 6 of arguments, filed 7/10/06, with respect to objection of claim 14 under 37 CFR as being in improper form, Applicants amendment of the claim to "embryonic stem" has been fully considered and is persuasive. The objection of 14 has been withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Applicant's arguments, see page 8 of the arguments, filed 7/10/06, with respect to the rejection of claim 14 under 35 U.S.C. 112, 2nd paragraph, as being insufficient antecedent to limitation of the claim, Applicants amendment of the claim to "embryonic stem cells" has been fully considered and is persuasive. The rejection of 14 has been withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-8 and 14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic mouse whose genome contains a nucleic

acid encoding a mouse cardiac alpha myosin heavy chain including a substitution of loop 1 of mouse cardiac alpha myosin heavy chain by a non-mouse myosin heavy chain loop 1 (ATPase loop), comprising of pig/rat β MHC loop 1 substitution and the interactive micro-domain of said cardiac alpha myosin heavy chain thereby, reducing an ADP dissociation rate of said mouse cardiac alpha myosin heavy chain, wherein said mouse cardiac alpha myosin heavy chain exhibits : (a) reduced contractility (speed of contraction); and (b) increased power generating capability (work capacity) resulting in a transgenic mouse exhibiting a reduced heart rate, does not reasonably provide enablement for a transgenic mouse wherein said substitution comprises an S342G mutation in said loop. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1-5 and 14 embrace a transgenic mouse characterized by a reduced heart rate having incorporated into its genome a transgene comprising a nucleic acid, which encodes a mouse cardiac alpha myosin heavy chain including a modification which reduces electrostatic interaction between loop 1 (ATPase) and the interactive micro-domain of cardiac alpha myosin heavy chain thereby reducing an ADP dissociation rate of said mouse cardiac alpha myosin heavy chain wherein said mouse cardiac alpha myosin heavy chain exhibits: (a) reduced contractility (speed of contraction); and (b) increased power generating capability (work capacity) resulting in the transgenic mouse exhibiting a reduced heart rate. Dependent claims limit the modification to an S342G mutation in loop 1 wherein modification comprises a substitution of loop 1 of mouse cardiac alpha myosin heavy chain by a rat or pig or human beta myosin heavy chain loop 1 (ATPase loop).

Claims 6-8 encompass a method of studying molecular and cellular aspects associated with said transgenic mice or a method for identifying compounds useful for treating or

preventing cardiac disease or a method for evaluating the effects of external factors selected from the group consisting of diet, exercise and combinations thereof on cardiac disease.

As a first issue, the claims embrace a transgenic mouse overexpressing a transgene comprising a nucleic acid, which encodes a mouse cardiac alpha myosin heavy chain including a modification which reduces electrostatic interaction between loop 1 (ATPase loop) and interactive micro-domain of cardiac alpha myosin heavy chain thereby reducing an ADP dissociation rate of mouse cardiac alpha myosin heavy chain. The specification in example I describes that the kinetic properties of myosins encoded by the same MHC isoform gene but derived from different species (e.g. pig, or human β versus rat β), can exhibit greater functional differences than those between distinct phenotypes (α versus β) originating from the same species) (specification p 14). The specification contemplates that in general, the ser at position 342 in mouse a myosin is mutated to a gly and the mutant construct then introduced into a mouse line using standard transgenic techniques and the resulting transgenic mouse is predicted to have slower speed, greater power and reduced heart rate better resembling larger mammals (specification p 16, lines 9-11). However, the specification has failed to provide guidance and/or working examples correlating to the creation of a transgenic mouse expressing a mouse cardiac alpha myosin heavy chain comprising an S342G mutation, which reduces electrostatic interaction between loop 1 (ATPase loop) and interactive micro-domain molecule wherein said mouse cardiac alpha myosin heavy chain exhibits: (a) reduced contractility (speed of contraction); and (b) increased power generating capability (work capacity) and exhibiting a reduced heart rate. One of skill in the art could not rely on the transgenic art to make such a transgenic mouse phenotype because neither the art nor the specification teach said transgenic mouse. The state of the transgenic art has set forth that phenotypes resulting from expression of a transgene are unpredictable. This is because the art of transgenic animals has for many

years stated that the unpredictability lies with the site or sites of integration of the transgene into the target genome. Transgenic animals are regarded to have within their cells cellular mechanisms, which prevent expression of the transgene, such as DNA methylation or deletion from the genome (**Kappell et al,** Current Opinion in Biotechnology 3:548-553, 1992) (p 549, col. 2, 2nd paragraph). The elements of the particular construct used to make transgenic animals are held to be critical, and that they must be designed case by case without general rules to obtain good expression of a transgene; e.g., specific promoters, presence or absence of introns, etc. (**Houdebine,** J. Biotechnology, 34: 269-287, 1994) (p 281). **Sigmund** (2000) states that the random nature of transgene insertion, resulting founder mice can contain the transgene at a different chromosomal site, and that the position of the transgene effects expression, and thus the observed phenotype (Sigmund (2000) Arteroscler. Throm. Vasc. Biol. 20, page 1426, col. 1, 1st paragraph, lines 1-7). Given the lack of guidance and relevant teachings provided by the specification with respect to the unpredictable nature of phenotypes resulting from a transgenic mouse whose genome comprises a nucleic acid sequence encoding a mouse cardiac alpha myosin heavy chain containing a modification wherein said modification comprises an S342G mutation in mouse cardiac alpha myosin heavy chain, which reduces electrostatic interaction between loop 1 (ATPase loop) and interactive micro-domain of cardiac alpha myosin heavy chain, it would have required undue experimentation for the skilled artisan to make and use the transgenic mouse embraced by the claims.

Claims 6-8 are directed to methods of studying molecular and cellular aspects associated with a transgenic mouse having a reduced heart rate, identifying compounds useful for treating and preventing cardiac disease of a transgenic mouse or a method for evaluating the effects of external factors selected from the group consisting of diet, exercise and combinations thereof on cardiac disease of a transgenic mouse. The specification

contemplated the transgenic mammals of the invention provide methods to study the molecular and cellular aspects of heart muscle disease and heart failure diseases (specification, p 9). For instance, a transgenic animal of the present invention may be sacrificed, and the cells and/or tissues examined at the cellular or molecular level and compared to cells and/or tissues from transgene-negative littermates. In addition, the specification contemplates the transgenic animals of the invention may be used to study the effects of overexpression of mutant alpha myosin heavy chain (MHC). For example, the effects of overexpression of alpha MHC on heart morphology and function, myocyte morphology and function, the expression of other molecules, the development and treatment of heart muscle disease and heart failure, can be evaluated. Furthermore, the specification contemplates the transgenic animals of the invention provide methods to test drugs candidates for prevention or treatment of heart muscle disease and heart failure. In addition, instant invention claimed transgenic mammals to study the effects of external factors on heart muscle disease and heart failure such as diet and exercise (specification p 11). However, neither the specification nor the art of record provide guidance and /or working examples for the claimed methods. The specification has failed to provide specific guidance and/or working examples of what types of specific molecular and cellular aspects are associated with claimed transgenic mouse. The specification failed to provide a transgenic mouse with a reduced heart rate phenotype which phenotype is correlated to a specific heart disease in order to study molecular and cellular aspects associated with heart diseases or to identify any compounds for either treatment or prevention of a cardiac disease or evaluating the effects of diet or exercise and combinations thereof on any cardiac disease. Given the lack of guidance by the specification correlating a transgenic mouse with reduced heart rate phenotype and cardiac disease treatment or drug efficacy on any cardiac disease it would have required undue experimentation to practice the invention as claimed for treating

cardiac diseases by overexpression of mutant alpha MHC gene without a reasonable expectation of success.

As a final issue, claims 1-5 and 14 embrace a homozygous or heterozygous transgenic mouse with a reduced heart rate. However, the specification has not provided working examples correlating homozygous transgenic mouse with reduced heart rate phenotype to heterozygous transgenic mouse. It is well known in the art that heterozygous mice because they carry one copy of the wild type allele do not always exhibit phenotype similar to knock out mice.

Therefore, in view of the quantity of experimentation necessary to determine the parameters for the production of a transgenic mouse with a modification comprising an S342G mutation comprising a substitution of loop 1 of mouse cardiac alpha myosin heavy chain by a non-mouse myosin heavy chain loop 1and the unpredictable state of the art for the production of said transgnenic mouse correlating to a phenotype with reduced contractility, increased power generating capability resulting in a transgenic mouse with reduced heart rate, and particularly correlating a transgenic mouse with reduced heart rate phenotype and cardiac disease treatment or drug efficacy on any cardiac disease, it would have required undue experimentation for one of skilled in the art to make and/or use the claimed transgenic mouse.

Applicant's arguments filed on 7/10/06 have been fully considered but they are not persuasive. Applicants argue that the specification, describes the cloning of the mouse a MHC gene, the transformation of mouse embryonic stem cells, and further the generation of transgene-carrying ES cell, the microinjection of the clones into blastocysts, the production of chimeric mice and the resulting homozygous offsprings generated by the mating of the chimeras (arguments p 6). Applicants also argue that the University of Wisconsin-Madison (UW) provides

a transgenic animal facility to serve faculty in need to study transgenic animals. Applicants further provide web sites for transgenic core facilities and commercial ventors, thus the specification fully describes the material necessary for the production of a transgenic animal (arguments p 7).

In response this is not found persuasive because enablement is not the issue of the methodology of making the transgenic mouse rather the issue is the unpredictability to produce the phenotype of the claimed transgenic mouse. In the instant case, the issue is to the unpredictable nature of phenotypes resulting from a transgenic mouse whose genome comprises a nucleic acid sequence encoding a mouse cardiac alpha myosin heavy chain containing a modification wherein said modification comprises an S342G mutation in mouse cardiac alpha myosin heavy chain, which reduces electrostatic interaction between loop 1 (ATPase loop) and interactive micro-domain of cardiac alpha myosin heavy chain. In addition, in the instant case the issue is to the unpredictability of correlating a transgenic mouse with reduced heart rate phenotype and cardiac disease treatment or drug efficacy on any cardiac disease.

Applicants herein refer to the declaration of Richard L. Moss, Ph.D., Chairman of the University of Wisconsin Department of physiology and co-inventor on the instant invention attached hereto as Exhibit 2. As described in Dr Moss declaration the transgenic mouse Exhibit 2, Figure 1 S341G KO PCR and S342G WT PCR results obtained from PCR-based genotyping designated to identify the S341G gene in the transgenic mice and figures 2A and 2B depicting the graphs plotting the rate force redevelopment of Wt and S341G transgenic mice does not correlate to the Table A showing the absolute force generated by the S342G transgenic mice and the wild type control and to the Table B showing the heart rate of the S342G transgenic and the wild type control. Hence the declaration cannot support enablement for the production of a

transgenic mouse whose genome comprises a nucleic acid sequence encoding a mouse cardiac alpha myosin heavy chain containing a modification wherein said modification comprises an S342G mutation in mouse cardiac alpha myosin heavy chain, which reduces electrostatic interaction between loop 1 (ATPase loop) and interactive micro-domain of cardiac alpha myosin heavy chain as claimed in the instant application.

Finally, Applicants argue that it is well accepted in the art that a transgenic mouse strain is by definition homozygous and Applicants provide websites for reference and attached Exhibit 4 for the Examiner's convenience if the strain is not homozygous for the desired gene, then any mating with another mouse would only have a 1:4 chance of receiving the desired transgene and therefore, would not breed true and thus could not be considered a "strain" (arguments p 9). Applicants further argue that in the current instance, the offspring of the implanted female will be heterozygous and are mated to wild type animals and this mating results in a litter that is either wild type or heterozygous for the transgene (arguments p 9). Applicants also argue that the heterozygotes are then crossed that result in a litter that is 1:4 homozygous for the transgene, following standard Mendelian genetics (arguments p 9).

In response this is not found persuasive because enablement is not he methodology of producing the claimed transgenic mice but the unpredictability of producing the claimed transgenic mice with a modification comprising an S342G mutation that correlates to a phenotype with reduced heart rate as discussed above. Further the claims are to a mouse not a strain.

As such, the rejection of claims 1-8 and 14 are maintained.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571) 272-3305. The examiner can normally be reached on Monday through Friday from 9:00 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram R. Shukla, can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

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